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Longitudinal Assessment of Mental Health Disorders and Comorbidities Across 4 Decades Among Participants in the Dunedin Birth Cohort Study

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KEY POINTS (93words)

Question:

Do mental-disorder life-histories shift among different successive disorders?

Findings:

In this longitudinal cohort study of 1037 participants in the Dunedin Study birth cohort, with assessments from 11 to 45 years of age, mental-disorder life-histories shifted among different successive internalizing, externalizing, and thought disorders. Mental-disorder life-histories are better described by age-of-onset, duration, and diversity of disorder than by any diagnosis.

Meaning:

The finding that most mental-disorder life-histories involve different successive disorders helps to account for genetic and neuroimaging findings pointing to transdiagnostic etiologies, and cautions against over-reliance on diagnosis-specific research and clinical protocols.

TWEET (191 characters with spaces)

Tracking 1000 people's mental health for 4 decades reveals frequent shifts across different successive disorders, raising the question: why study or treat mental disorders one at a time if most disorders share common causes?

STRUCTURED ABSTRACT (340 words)

Importance: Mental-health professionals typically encounter patients at one point in patients' lives. This cross-sectional window understandably fosters focus on the current presenting diagnosis. Research programs, treatment protocols, specialist clinics, and specialist journals are oriented to presenting diagnoses, on the assumption that diagnosis informs about etiology and prognosis. We tested an alternative hypothesis: people with mental disorder experience many different kinds of disorders across diagnostic families, when followed for 4 decades.

Objective: To describe mental-disorder life-histories across the first half of the life course.

Design: Population-representative 1972-1973 Dunedin Study birth cohort.

Setting: New Zealand.

Participants: Observed from birth to age-45 years (until April, 2019).

Main Outcomes and Measures: DSM-diagnosed impairing disorders were assessed nine times from age 11-45 years. Brain function was assessed through age-3 neurocognitive examinations, childhood and adulthood neuropsychological testing, and midlife neuroimaging-based estimated brain-age. Analysis was performed May-January, 2019-2020.

Results: Of 1037 original participants (535[51.6%] male), 1013 had mental-health data. At age 11-15 years, 35% (346/975) met criteria for a mental disorder, 50% (473/941) at age 18, 51% (489/961) at 21, 48% (472/977) at 26, 46% (444/969) at 32, 45% (429/955) at 38, and 44% (407/927) at 45. Disorder onset by adolescence for 59% (600/1013) of participants, eventually affecting 86% (869/1013) of the cohort by midlife. By age 45, 85% (737/869) of participants with disorder accumulated comorbid diagnoses. Participants with adolescent-onset disorder subsequently presented with disorder at more past-year assessments (r=.71[95%CI:.68,.74],

p<.001) and met criteria for more diverse disorders (r=.64[95%CI:.60,.67], p<.001). Confirmatory factor analysis summarizing mental-disorder life histories across four decades identified a general factor of psychopathology, labelled the *p-factor*. Longitudinal analyses showed that high scores on *p* (indicating extensive mental-disorder life-histories) were antedated by poor age-3 neurocognitive functioning, r=-0.18 (95%CI:-0.24,-0.12), accompanied by child-to-adult cognitive decline, r=-0.11 (95%CI:-0.17,-0.04), and associated with older brain-age at midlife, r=0.14 (95%CI:0.07,0.20).

Conclusions and relevance: Mental-disorder life-histories shift among different successive disorders. Data from the present study, alongside nationwide data from Danish health registers, inform a life-course perspective on mental disorders. This perspective cautions against over-reliance on diagnosis-specific research and clinical protocols.

Introduction

The practice of diagnosing mental disorders is at a crossroads. The Diagnostic and Statistical Manual of Mental Disorders (DSM) [1-4], which guides diagnostic practice, is being questioned [1]. The U.S. National Institute of Mental Health has called for a new approach to studying mental disorders [2]. And the public is confused about what constitutes a mental disorder, resulting in "diagnosis shopping"[3]. Our thesis is that progress in conceptualizing mental disorders has been delayed by the field's limiting focus on cross-sectional information. This article demonstrates how much novel information can be learned by taking a longitudinal, life-course view of mental disorders.

Researchers and clinicians in mental-health fields typically encounter a patient at one point in the patient's life, and, accordingly, tend to study or treat the disorder(s) that can be diagnosed at that time. This short-term view promotes the idea that patients can be adequately characterized by their current presenting diagnoses. Research hypotheses and clinical protocols tend to be diagnosis-tailored, resulting in diagnosis-specific therapies, clinics, journals, and professional societies, and even diagnosis-specific funding agencies. Such tailoring is based on the assumption that a diagnosis provides information about the etiology of the patient's disorder, and about tailoring treatment to ensure good response and prognosis. However, the wisdom of over-emphasizing a diagnosis is challenged by new evidence from neuroimaging studies[4-8], genetic studies[9-11], and risk-prediction studies[12-14] that reveal that major etiological findings are transdiagnostic. Moreover, since DSM-III[15], evidence has accumulated that sets of disorders/symptoms predictably co-occur[16,17]. Depression and anxiety disorders emerge in the same patient (the Internalizing family); disruptive disorders and substance abuse emerge in the

same patient (the Externalizing family); and disorganized thoughts, delusional beliefs, hallucinations, obsessions and compulsions emerge in the same patient (the Thought Disorder family). As a result of such empirical studies about the structure of psychopathology, these disorder families are now accommodated in research[18] and transdiagnostic treatments are gaining steam[19].

Of note, most research on the structure of psychopathology has been conducted using data collected at one time point. But what if most patients tend to meet criteria for many different diagnoses in turn, not only within one diagnostic family, but across families too? What if the predominant pattern were one in which mental disorder onsets in the first decades of life, and thereafter, whenever an individual is assessed for disorder, that individual might meet criteria for a succession of different diagnoses? These questions are of pragmatic significance because much of the work of mental-health professionals is driven by cross-sectionally-assessed diagnoses.

One remarkable study confirmed that most patients do meet criteria for many different diagnoses in turn. In that study, every mental disorder diagnosed brought increased risk that the patient would be diagnosed at another time with other disorders inside, but also outside, the index disorder's family[20]. Using Danish registers of in-patient and out-patient clinics, the study covered nearly two decades and included nearly six million individuals. Nevertheless, Berkson's bias could exaggerate the picture of comorbidity in these registers, as greater comorbidity and duration of impairment determine greater likelihood of treatment; patients in clinical registers are typically unusually complex cases who have many comorbid disorders lasting many years[21,22]. Registers omit patients treated in primary care and also the many

community-dwellers whose disorder goes untreated. Thus, it is possible that crossing diagnostic families is unique to clinic patients but does not generalize to the fuller population of individuals experiencing mental disorder. Another potential artifact in clinic registers is the possibility of inconsistent diagnostic practices by a series of clinicians seeing the same patient at different times. Here we report a replication and extension of research begun in Danish registers, using a population-representative birth cohort whose mental health has been tracked regardless of treatment status, and repeatedly assessed in a systematic, standardized manner for four decades.

The cohort that we tracked, the Dunedin Study, is unique in the annals of psychiatric epidemiology. In 1983-84, when participants were 11 years old, it was the first cohort to measure disorders using standardized diagnostic interviews[23]. Research diagnoses have been made on nine occasions with strong participant retention, until participants turned age 45 in 2018-19. This diagnostic time-series allowed us to describe mental-disorder life-histories in terms of three developmental parameters: age-of-onset, duration, and comorbid diversity among disorder families. We then applied confirmatory factor analysis to symptoms to summarize participants' mental-disorder life-histories with a general factor of psychopathology (which has been previously described and replicated[24,25]). We tested the hypothesis that mental-disorder life-histories, summarized by a general factor of psychopathology, reflect compromised brain function, by examining associations with age-3 neurocognitive deficits, subsequent cognitive decline from childhood to adulthood, and advanced brain-age in midlife, as derived from neuroimaging.

Method

Sample (**eMethods 1**).

Participants were members of the Dunedin Study, a longitudinal investigation of a population-representative birth cohort. The 1,037 (535[52%] male) participants were all individuals born between April 1972-March 1973 in Dunedin, New Zealand (NZ), who participated in the first assessment at age 3 years[26], representing 91% of participants who were eligible based on residence in the province. The cohort represented the range of socioeconomic status on NZ's South Island, and in adulthood matched the NZ National Health and Nutrition Survey on key health indicators (e.g., BMI, smoking, physician visits) and same-age citizens in the NZ Census on educational attainment [26,27]. The cohort is primarily white (93%), matching South Island demographics. Assessments were held at birth and ages 3,5,7,9,11,13,15,18,21,26,32,38, and most recently, 45 years, when 94% (938) of the 997 living cohort members took part. Participants gave written informed consent. Protocols were approved by the institutional ethical review boards of participating universities.

Assessing psychopathology (**eMethods 2**).

Beginning at age 11, participants were interviewed about past-year symptoms of mental disorders. Interviews were conducted by health professionals, not lay interviewers. Interviewers were kept blind to participants' prior data. At ages 11,13, and 15, interviews were carried out with the Diagnostic Interview Schedule for Children-Child Version[28], assessing these disorders: Externalizing (ADHD, Conduct Disorder) and Internalizing (Depression, Anxiety and Fears [including Separation Anxiety, Overanxiety, Social Phobia, Simple Phobia]). At ages 18,21,26,32,38, and 45, interviews were carried out with the Diagnostic Interview Schedule[29,30], assessing these disorders: Externalizing (ADHD, Conduct Disorder, Alcohol Dependence,

Cannabis Dependence, Other Drug Dependence, Tobacco Dependence), Internalizing (Depression, Generalized Anxiety Disorder, and Fears [Social Phobia, Simple Phobia, Agoraphobia, Panic Disorder], PTSD, Eating Disorders [Bulimia and Anorexia]), and Thought disorders (Obsessive-Compulsive Disorder, Mania, Schizophrenia). As previously reported[31], a Correlated-Factor Model showed that this three-factor structure provided an excellent fit to the symptom-level data. Diagnoses, which followed DSM exclusionary criteria, were based on symptom algorithms and impairment ratings, but also incorporated information including standardized teacher/parent/informant reports as developmentally appropriate, psychiatrists' review of interviewers' detailed case notes, pharmacists' medication review, and staff ratings of symptoms observed[32]. Up to age 15, diagnoses were made according to DSM-III[33]; at ages 18 and 21, according to DSM-III-R[34]; at ages 26,32, and 38, according to DSM-IV[35]; at age 45 according to DSM-5[36], with the exception of substance-dependence disorders, which were diagnosed according to DSM-IV because DSM-5 dropped the dependence/abuse distinction. Review of treatment in the years between Study assessments indicated that our net of 9 past-year diagnostic interviews captured all but 17 individuals treated in the 4 decades, most of whom had post-partum depression or were treated by a family doctor for anxiety/depression.

Assessing brain function (eMethods 3).

Brain Health at age 3 years, a composite measure, was derived from a 45-minute examination that included assessments by a pediatric neurologist, standardized tests of cognitive function, receptive language, and motor skills, and examiners' ratings of emotional/behavioral regulation.

Cognitive function was measured at ages 7,9, and 11 years using the Wechsler Intelligence Scale for Children–Revised (WISC-R)[37] and at age 45 years using the Wechsler Adult Intelligence Scale–IV (WAIS-IV)[38]. Cognitive decline was tested by predicting IQ at midlife after controlling for IQ in childhood.

Brain-age at age 45 years was estimated using a publicly available algorithm[39] that integrated structural neuroimaging measures of cortical thickness, cortical surface area, and subcortical volume to estimate the age of a person's brain relative to their chronological age. T1-weighted structural images were acquired using a Siemens Skyra 3T equipped with a 64-channel head/neck coil.

Statistical analysis.

Raw visualization of diagnostic data was followed by cross-tabulations of mental disorders within and across time, reporting frequencies/percents and 95%CIs. Sankey diagrams were used to depict shifts in diagnosis across time. Confirmatory factor analysis was used to model the structure of psychopathology using symptom-level data (**eMethods 4**). Associations between variables were reported as sex-adjusted Pearson's r (with 95%CIs). All 10 association tests reported were significant after Bonferroni correction, $p < .005$.

Results

Longitudinal patterns of mental disorder

Of 1037 original participants (535[51.6%] male), 1013 had mental-health data. At age 11-15 years, 35% (346/975) met criteria for a mental disorder, 50% (473/941) at age 18, 51% (489/961) at 21, 48% (472/977) at 26, 46% (444/969) at 32, 45% (429/955) at 38, and 44% (407/927) at 45.

Figure 1 visualizes the raw data for the 1037 original cohort members, followed from age 11 to 45 years. The figure reveals three patterns. First, most participants were first diagnosed by the Study as a teenager (bottom left, Figure 1). Approximately one-third (34%, 346/1013) of the cohort experienced first-onset disorder by age 15; nearly two-thirds (59%; 600/1013) by age 18. Virtually no participants were diagnosed for the first time at the age-45 assessment (**Figure 2A).** Second, early onset was associated with more years with disorder and more comorbid disorders (left-to-right, Figure 1). Regarding duration, participants with early-onset disorder tended to subsequently meet diagnostic criteria at more past-year assessments (r=.71[95% CI:.68,.74], p<.001; **Figure 2B**). Regarding comorbidity, participants with early-onset disorder tended to subsequently meet criteria for more diverse disorder types (r=.64[95% CI: .60,.67], p<.001; **Figure 2C**). These associations remained after correction for n years available for observation between first onset and study end (**eMethods 2**). Third, almost everyone eventually experienced disorder (top right, Figure 1). Cumulatively, by age 45, 86% (869/1013) of the cohort met criteria for at least one disorder. This seemingly high lifetime prevalence matches prevalence reports from multiple psychiatric-epidemiology studies around the world (**eMethods 5**).

Participants characterized by only one pure disorder were atypical. For example, among participants ever diagnosed with an Internalizing disorder (shown in blue, **Figure 3A**), most (70%, 503/712) also experienced Externalizing or Thought disorders and another 16% (113/712) had multiple kinds of Internalizing disorders. This left only 14% (96/712) of Internalizing participants who experienced only one pure type of Internalizing disorder such as Depression or one anxiety-disorder type. Of interest, 75% (72/96) of these participants met criteria for

disorder at only one assessment age. The same cross-family pattern was observed among participants ever diagnosed with an Externalizing disorder (in violet, **Figure 3A**); most (77%, 478/625) also experienced Internalizing or Thought disorders and another 11% (67/625) had multiple kinds of Externalizing disorders. This left only 13% (80/625) of Externalizing participants who experienced only one pure type of Externalizing disorder, such as ADHD or Cannabis Dependence. Of interest, 71% (57/80) of these participants met criteria for disorder at only one assessment age. Fewer than 2% (3/177) of Thought-disordered participants experienced only one pure type of Thought disorder: OCD, Mania, or Schizophrenia (in orange, **Figure 3A**). To approximate hospital-register data, we restricted this analysis to cohort members who had ever received inpatient treatment (N=83; **Figure 3B**); inpatients who had one exclusive diagnosis lifetime were virtually non-existent (**eMethods 6**).

The ebb and flow of mental disorders over decades

Cross-sectionally, Internalizing, Externalizing, and Thought disorder families co-occurred at every assessment (**eMethods 7**). Sequentially, participants with a disorder in any of the three diagnostic families at one specific age were at significantly higher risk for both other diagnostic families at subsequent ages, and all disorders predicted elevated risk for all other disorders (**eMethods 8**). Lifetime comorbidity thus accumulated from adolescence to age 45. At ages 11-15 years, 32% (110/346) of participants with disorder had comorbid diagnoses, but by age 45 85% (737/869) of participants with disorder had accumulated comorbid diagnoses (**eMethods 9**).

Figure 4A depicts the movement of participants in and out of diagnoses. Four findings stand out. First, the number of participants surviving to midlife without disorder diminished

with time, as shown by the progressively narrowing dark-green band (also seen in Figure 1). Second, intermittent remission occurred, as shown by paths leading into and out of light-green disorder-free periods. Third, there was some preservation of disorder across age; for example, the blue band shows continuity of Internalizing disorders and the violet band shows continuity of Externalizing disorders, between adjacent ages. Fourth, there was substantial movement between diagnostic families in every direction at every age, as shown by paths flowing between colors. Tracing all 1037 participants across time revealed 692 mental-disorder life-history patterns, of which 605 (87.4%) were unique to one person (**Figure 4A**). To approximate hospital-register data we restricted the analysis to participants who received inpatient mental-health services; movement between diagnostic families was even more pronounced among these 83 individuals (**Figure 4B**). Each participant with inpatient treatment followed a unique mental-disorder life-history pattern (**eMethods 10**).

Mental-disorder life-histories: onset-age, duration, diversity, and the *p-factor*

Participants' age-of-onset, duration in terms of number of assessment ages with disorder, and diversity of diagnoses were positively inter-correlated (onset-age with number of assessment ages, r=.71 [95%CI:.68,.74]; onset-age with comorbid variety r=.64 [95%CI:.60,.67]; number of assessment ages with comorbid variety, r=.83 [95%CI:.81,.85]; all p <.001). We used confirmatory factor analysis of symptom-level data to summarize participants' mental-disorder life-histories. A model that specified a general factor of psychopathology (hereafter termed '*p*') fit the dataset well and loadings on the *p*-factor were all positive and high, averaging 0.612 (all p's < .001) (**eMethods 4**). Participants with higher *p*-scores experienced younger age-of-onset

(r=.48, 95%CI:.43,.52), greater number of assessment ages with disorder (r=.69, 95%CI:.66,.72), and greater diversity of diagnoses (r=.76, 95%CI:.73,.78) (**eMethods 4**).

Mental-disorder life-histories and health of the brain

Children who grew up to score higher on the *p*-factor performed more poorly on age-3 neurocognitive examinations, r=-0.18 (95% CI:-0.24,-0.12) p<.001 (**Figure 5A**). Later in childhood, they tended to have lower WISC-R IQ, r=-0.19 (95% CI:-0.25,-0.13) p<.001. Their cognitive functions continued to decline, as revealed by lower WAIS-IV IQ at age 45 years relative to their childhood IQ, r=-0.11 (95% CI:-0.17,-0.04) p<.001 (**Figure 5B**). By age 45, participants with higher *p* scores tended to show older brain-age, r=0.14 (95% CI:0.07,0.20) p<.001 (**Figure 5C**). **Figure 5** shows that compared to cohort peers with the lowest *p* scores, participants with the highest *p* had brain health .61SD weaker, child-to-adult cognitive decline 3.8 IQ points steeper, and midlife brain-age 3.9 years older (**eMethods 11**.)

Discussion

Participants in this four-decade study of a population-representative cohort had mental-disorder life-histories that could not be adequately characterized by diagnosis at one point in time. This research advances knowledge in five ways. First, this study confirmed prior reports[40,41] that most individuals who experience mental disorder have first-onset as juveniles (34% before age 15; 59% before age 18). Second, it further confirmed the high lifetime prevalence reported by multiple longitudinal cohort studies that use repeated psychiatric assessments to counteract undercounting caused by retrospective-recall failure[42]; a previous review concluded that most of the population eventually experiences mental disorder, whereas people who sustain enduring mental health are rare exceptions (14% in our cohort). Third, we

replicated Danish-register findings that psychiatric-clinic patients tend to experience diverse disorders in turn, and every disorder predicts risk for every other disorder[20]. We expanded on that prior work by providing initial evidence that outside-family comorbidity is characteristic of the general population as well as registered patients. In contrast to assumptions of diagnosis-specific research and clinical protocols, we found evidence that virtually no one gets and keeps one pure diagnosis type. Fourth, this study applied a novel life-course approach to longitudinal data about mental disorders. Three key life-course parameters tended to converge in the same individuals: (a) younger onset of disorder, (b) more years' duration of disorder, and (c) more diverse types of comorbid disorder (even after controlling for years post-onset). A single dimension derived from all symptoms reported over multiple decades, termed the *p-factor,* summarized differences between individuals in their mental-disorder life-history. Fifth, these life-histories were antedated by compromised brain health in early childhood (whether genetically-inherited or acquired from adverse experiences), accompanied by cognitive decline from childhood to midlife, and associated with older "brain-age" measured via structural neuroimaging at midlife.

This research has limitations. First, findings come from a predominantly white sample, one country, and one historical period. However, previous mental-health findings from this cohort have replicated in other countries (see, e.g., evidence about lifetime prevalence[43] and the structure of *p*[24]). Moreover, this analysis replicated Danish-register findings[20]. Second, our analysis was left-hand censored at age 11 and right-hand censored at age 45. Third, Dunedin participants have lived from DSM-III to DSM-5; some disorders' criteria changed and interview questions were accordingly updated. As such, the findings reflect the changing health practices

during participants' lives. Fourth, and relatedly, the Study did not assess disorders that at the time were assumed to have very low base rates (e.g., childhood autism). Fifth, many analyses treated disorders as discrete categories, despite awareness that diagnostic thresholds are decision-making conventions. However, our analyses summarizing mental-disorder life-histories with the *p*-factor used symptom-level data, exploiting meaningful information above and below diagnostic thresholds. Sixth, although unreliability may influence diagnostic decisions both in research and in clinical practice, Dunedin's diagnostic reliability is sufficient for research and unreliability is not the reason we observe shifting among different successive disorders across the life course (**eMethods 8**). Moreover, the same findings emerge from Dunedin mental-disorder life-histories as from Danish registered discharge diagnoses.[20]

There are implications for public understanding. Mental disorder eventually affects almost everyone. Some mental-disorder life-histories resemble a fractured leg or influenza, disabling but short-lived. Other mental-disorder life-histories become chronic or recurrent. However, people meeting diagnostic criteria experience impaired functioning and many absorb health-care resources. Public psycho-education about the ubiquity of disorder could reduce stigma and promote earlier and increased treatment uptake, facilitating prevention. Rather than view mental disorders as rare, members of the general public should expect at least one bout of mental disorder in their lifetime.

There are implications for prevention. Juvenile onset was highly prevalent and it portended more years of disorder, greater diversity of comorbid disorders, and reduced likelihood of recovery, which were linked to cognitive decline and older structural brain-age by midlife. These findings advise directing more mental-health resources toward pediatric efforts

to prevent mental disorder, especially as only a minority of children with disorder receive effective treatment. Ubiquitous juvenile onset also means that newly presenting adult patients almost certainly experienced prior disorder (even if their memory fails them), and those disorders may have looked quite different from the current disorder. Of course, clinicians will not have the benefit of their patients being enrolled in a four-decade longitudinal study. An obvious caveat is that clinicians must treat the disorder that appears before them, offering relief for the patient's current complaint. The life-course approach thus has two clinical implications. First, looking to the past, it places priority on expert history-taking to support strategic treatment planning[44,45]. Second, looking to the future, because many patients will go on to experience diverse disorders, therapy cannot just mitigate the presenting symptoms, but must also build skills for maintaining enduring mental health. The life-course approach makes trans-diagnostic interventions high priority.

There are implications for etiological research. First, finding specific causes matched to specific disorders has been a research holy grail[46], but findings here suggest that causal specificity may be unrealizable because mental-disorder life-histories include diverse disorders. The life-history approach explains why genetic[9-11], neuroscience[4,6,7], and risk-factor research[13,42] point to shared etiologies underlying an array of disorders[47]. Second, our findings suggest that research can be misled by cross-sectional designs. Particularly problematic are case-control studies that enroll patients on the basis of the current disorder in their mental-disorder life-history (unaware of other past and future disorders), and compare them against currently-well controls (who may have been unwell in the past and may become unwell in the future[48]). A third implication is that etiological research might productively embrace dimensions that

quantify variation in mental-disorder life-histories. The findings here suggest that dimensions like onset-age, duration, diversity—or *p*—may reflect patients' lives (especially in inpatient settings) better than any particular differential diagnosis can.

Much research shows that sustained mental wellness is rare, and this study shows that presentation with only one diagnosis—and even one 'diagnostic family'--is rarer still, suggesting it may be time to adopt a life-course perspective on mental disorders. The life-course framework orients research away from the etiology of a single disorder at one point in time toward studying the dynamics of mental-disorder life-histories. We hope that the new findings reported here encourage research to design tools to assess an individual's life-course vulnerability to psychopathology; identify causes of this vulnerability; explain why this vulnerability manifests in different diagnoses at different points in the life course; and develop transdiagnostic preventions.

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Avshalom Caspi, Renate Houts, and Terrie E. Moffitt had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure legends

Figure 1. **The natural history of mental disorders in a cohort of 1037 individuals**.

The graph is made up of a thin line for each individual in the Dunedin Study stacked together to show the 1037 cohort members, followed from age 11 to age 45 years. Columns are assessment ages. Green signifies the absence of a mental disorder. Yellow signifies that an individual met criteria for a psychiatric diagnosis at a given assessment age; as the yellow deepens into orange and brown, it signifies a greater number of concurrent disorders diagnosed for that individual. Grey signifies that a Study member was missing at that assessment age. Black signifies that a study member had died.

Figure 2. **Early-onset mental disorders and their sequelae.**

Panel A shows the assessment age at which participants first met diagnostic criteria for a mental disorder. **Panel B** shows that early onset was associated with a greater likelihood of meeting diagnostic criteria at more subsequent 12-month assessment windows, up to midlife. **Panel C** shows that early onset was associated with meeting criteria for more different types of mental disorders in subsequent years, up to midlife.

Figure 3. Does anyone have just one exclusive diagnosis?

Panel A contains information about participants who were ever diagnosed by the Study with a mental disorder (N=869). The three bars depict the number of participants in the cohort with lifetime Internalizing, Externalizing, and Thought disorders, respectively. Each bar is divided according to whether, over their lifetime, these participants also met criteria for another

disorder outside that family of disorders; or met criteria for another disorder within that family of disorders; or met criteria for just a single disorder. **Panel B** restricts the analysis to cohort members who received inpatient mental-health services (N=83).

Figure 4. The ebb and flow of mental disorders.

The Sankey diagrams in Panels A-B show cohort members' shifting diagnoses from one assessment phase to the next, from ages 11-15 to age 45. The colors of the horizontal bands divide the diagram into different psychiatric statuses. The heights of the horizontal bands show the prevalence of different statuses at each assessment phase. **Panel A** contains information about the full cohort (N=1037). **Panel B** restricts the analysis to 83 participants who received inpatient mental-health services (8% of the cohort). Note: it is possible to follow groups across contiguous adjacent assessments, not across the entire panel.

Figure 5. **The origins and sequelae of the *p-factor***.

Compromised brain health at age 3 years was associated with higher *p* (**Panel A**). Higher *p* was associated with more decline in cognitive ability from childhood to adulthood (**Panel B**), and older brain-age by midlife (**Panel C**). In each panel, the *p* factor is standardized to a mean of 100 (SD=15), and higher *p* scores indicate more generalized psychopathology. In Panels A and C, the bars of the histograms graph the percentages of the sample at different levels of the *p*-factor. The squares and standard error bars show the mean scores of individuals as a function of *p* scores less than < 85 (N=163), 85 to 95 (N=237), 95 to 105 (N=259), 105 to 115 (N=189), 115 to 125 (N=91), and > 125 (N=61); these groups have been clumped solely for graphing purposes

(with group N>50). The regression lines show the association between the *p*-factor and its childhood correlates and adult sequelae. The regression coefficients reported in the text are based on the full distribution of *p* scores (see **eMethods 11** for scatterplots).